Review Article

A Review on Novel Repurposing Candidates; Focus on Improved Therapeutic Strategies to Treat Myocardial Infarction

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ABSTRACT

There has been revival of interest over the couple of decades in reconstructive therapy using existing drug candidates to treat various cardiovascular diseases. In contrary, it becomes necessary to probe the current ideas to bridge the gap between clinical recommendations and the treatment and to gain insights into the various barriers to comprehensive risk reduction; a situational analysis is required to describe the current standard of care for Cardiovascular Disease. This bought up substantial changes in perspective therapeutic approach to treat patients with acute myocardial infarction. One of such approaches to ascertain the novel therapeutic indication for already existed drug is called 'drug re-profiling'. Identifying the safety and tolerability of new chemical entity in research and development process takes long time and huge cost with low success rate. This brings non-linearity in drug development process. This review discusses insights into novel candidates for drug repurposing and their part in reconstructing the architectural damages in both infracted and non-infracted myocardium. And also highlights their central role in drug development process for time efficient and cost-effective strategies than de novo design approach as the approved drug information regarding pharmacokinetics, side effects and drug interaction are collected during all phases of clinical trials.

Keywords: Myocardial infarction, Drug repurposing, Anti-diabetic, Anti-depressant and Anti-inflammatory.

INTRODUCTION

Cardiovascular diseases are a heterogeneous group of cardiac disorder which involves Coronary Heart Disease, Myocardial Infarction, Heart Attack, Rheumatic Heart Disease, Hypertension, Congenital Heart Disease.[1] According to American heart association, cardiovascular diseases accounts for 17.3 million deaths/yr and by 2030 it is expected to grow more than 23.6 million deaths every year.[2] Among all the cardiac disease myocardial infarction accounts for 9 million deaths/year and is one of the major cause of global mortality.[3] Similarly, in UK 63% of Myocardial Infarction (MI) patients develop heart failure within 6 years.[4] Even in India, WHO estimated that CVD is the largest cause of deaths in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually.[5]

Myocardial Infarction:

Myocardial Infarction associated with necrosis of cardiao myocytes in the myocardium region caused by ischemia, due to perfusion imbalance between oxygen supply and demand of blood to the heart via the coronary circulation. Myocardium, the middle layer of heart is supplied with blood by coronary arteries. Death of myocardial muscle occurs due to insufficient blood supply to the myocardium which results in ischemia of the myocardium.[6] There are many modified and non-modified risks factors of MI which includes alcohol consumption, smoking, diabetes mellitus, family history, dyslipidamia, stress, hypertension etc.[7]

Pathophysiology of MI includes many mechanisms like thrombus formation, atherosclerosis that involves release of pro-inflammatory mediators like NF-kβ, interleukin-6, monocytes, interferon-γ and reactive oxygen species sand reactive nitrogen species generation.8 It also increases cardiac biomarkers such as Total creatine phosphokinase (CPK), CPK-isoenzyme-MB (CPK-MB), lactate dehydrogenase (LDH), Troponin-I etc.9 Thrombus formation and release of inflammatory mediators contributes to the obstruction of blood vessel and that leads to imbalance between oxygen demand and supply. This imbalance in blood vessel and ROS generation both leads to ischemia and ultimately MI.[6]

To combat against diseases, conventional drug discovery methods involve more scientists who spent huge time to discover a drug for therapeutic.[10] Moreover, development of new drugs demands eternity, high-costs and also success rate of approval is less based on safety and tolerability profiles of new drug.

Drug re-positioning:

Drug repurposing being a emerging strategy for recognizing a new indication for already subsisting drugs and compounds. Moreover, it reduce cost-effective and time-consuming for developing new drug, also they are prove to be safe in human.[11] It focuses on already marketed drugs. Serendipitous observation helps to identify suitable drug candidates and its new indication. This review highlights drugs suited for repurposing in Acute Myocardial Infarction. There are many drugs which have been re- positioned for new indications.

REPURPOSED DRUG CANDIDATES TO TREAT MI

Paroxetine

It is an selective serotonin reuptake inhibitor, anti-depressent drug.[13] Elevated norepinepherine causes increase in heart rate and cardiac output, prolonged activation of sympathetic nervous system leads to heart failure.[14,15] As the catecholamine levels increased in the circulation there will be dysregulation of G protein (heterotrimeric guanine nucleotide–binding protein)–coupled receptor (GPCR) in the heart which leads to progression of heart failure. GPCR kinases activates due to increased stimulation of β-adrinergic receptor (βAR) leads to phosphorylation and down regulation of βAR level signalling leads to a loss in inotropic reserve.[16] Increased level of GPCR kinase 2 (GRK2) in the heart can cause adverse remodelling and contractile dysfunction during heart failure. HF can be prevented by inhibiting GRK2 through C-terminal peptide which obstructs binding of GRK2 to Gβγ.[17] GRK2 play a major role in apoptosis after cardiac injury.[18] Paroxetine(5mg/kg per day) administration to mice inhibited GRK2 and improved the cardiac function by improving left ventricle ejection fraction 30% and 20% absolute increase in fractional shortening. Its beneficial effects are greater than those of β-blocker therapy. Hence it represents a potential repurposed drug to treat MI.[19]

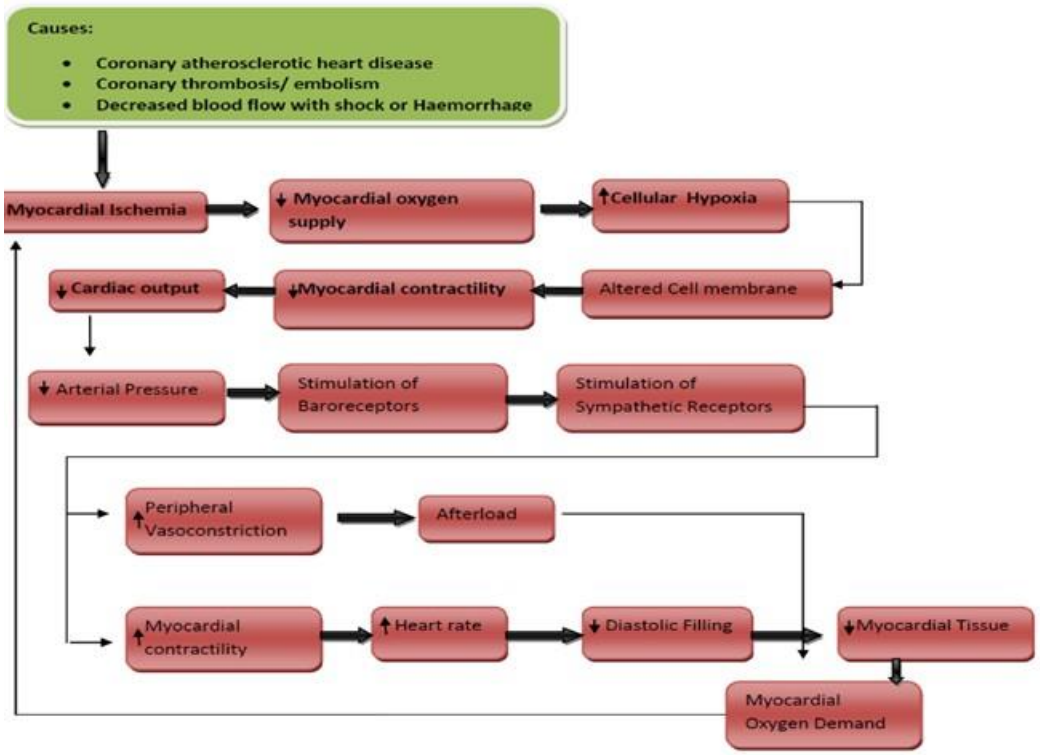

Figure 1: Pathophysiology of Myocardial Infarction

Table 1: Adverse effect of current drugs used in the treatment of MI.[6]

Class of drugs	Examples	Adverse effects
Angiotensin Converting Enzyme Inhibitors (ACEI)	Benazepril, Captopril, Enalapril and Fosinopril	Hyperkalaemia, Hypotension, Angioedema, rash, Proteinuria, Renal failure, Neutropenia and Cholestasis
Beta-blockers	Metoprolol, Atenolol, Esmolol and Betaxolol	Less bradycardia and dyslipidaemia
Thrombolytic Agents	Streptokinase, Tenecteplase and Urokinase	Hemorrhagic stroke
Antiplatelet Agents	Aspirin	GI irritation
Nitrates	Nitroglycerin	Headache and Tachyphylaxis
Analgesics	Morphine, Meperidine and Nalbuphine	Hypotension and Respiratory depression

Table 2: Established drugs repositioned for new indications.[12]

DRUGS	CURRENT TREATMENT	NEW INDICATION
Tamoxifen	Breast cancer	Acute Coronary Syndrome
Metformin	Diabetes	Breast cancer
Chlorimipramine	Anxiety disorders	Glioma and Colorectal cancer
Propranolol	Beta-blocker	Osteoporosis and Melanoma
Allopurinol	Tumourlysis syndrome	Gout
Amphetamines	Asthma, Depression and Fatigue	Hyperactivity disorder
Amphotericin	Fungal Infections	Leishmanaiasis
Acetylsalicylic acid	Inflammation and Pain	Colorectal cancer
Bimatroprost	Glaucoma	Eyelash growth
Cymbalta	Antidepressant	Fibromyalgia
Doxepin	Antidepressant	Antipruritic
Finasteride	Benign Prostate Hyperplasia	Male Alopecia
Gemcitabine	Viral Infections	Cancer
Hydroxychloroquine	Anti-parasitic	Arthritis
Ibuprofen	Rheumatoid arthritis	Parkinson's disease
Mifepristone	Pregnancy termination	Cushing's syndrome
Fluoxetin	Antidepressant	Premenstrual Dysphoric Disorders
Minoxidil	Anti-hypertensive	Hair loss
Thalidomide	Nausea and morning sickness in pregnant women	Multiple Myeloma
Tofranil	Anti-depressant	Bed wetting
Sildenafil	Pulmonary arterial hypertension	Erectile dysfunction

Colchicine

It is an anti- inflammatory drug[20] used to treat Mediterranean fever and Acute gouty arthritis.[21] Based on its mechanism of action, investigation has been conducted in the field of Rheumatology and Cardiology. NACHT-LRRPYD-containing protein 3(NALP3/ NLRP3) is a protein present in the human body, this protein also known as cryopyrin which is located in the chromosome which encodes NLRP3 gene. NLRP3 promotes Interleukin-1 β(IL-1 β) which mediates progression of artherosclerosis, adverse cardiac remodelling and heart failure.[22,23] Secondary prevention of heart failure detected with low dose of colchicine.[24] Patients having acute coronary syndrome, administration of Colchicine (1.5mg) during cardiac catheterization can reduce myocardial production of IL-1 β(activates inflammation in myocardium). Colchicine 1.5mg followed by 0.5mg 1hour later and 0.5mg twice daily for 5 days protects the heart from MI by reducing infarct size and also inhibits NALP3. Hence chlochicine has been successfully reported as an repurposed drug to treat MI.[21]

Donepezil

It is an Acetylcholinesterase inhibitor used for the treatment of Alzheimer's disease.[25] Matrix metalloproteinase (MMP-9) localized at the left ventricular infarct area were large number of inflammatory cells including macrophages infiltrated. Severe inflammatory cells activates MMPs which degrades the collagen network and weaken the tensile strength of the myocardium, resulted in wall repture.[26] The production of Pro-inflammatory cell and other immune cell were inhibited by Acetylcholine which is released by efferent vagus nerve through electrical signals.[27] Chronic vagal nerve stimulation prevents cardiac pumping dysfunction and improves the survival rates in rats with heart failure after large MI.[28] Thus 'cholinergic' anti-inflammatory pathway provide a therapeutic strategy to treat various inflammatory diseases (Pavlov *et al.*, 2006).[27] Donepezil, an acetylcholinesterase inhibitor reproduce the effect of vagal nerve stimulation. By enhancing vagal activity it prevent cardiac remodeling in rat MI model.[29] Lipopolysaccaride (LPS) 10mg/ml administration to mice increases macrophage MMP-9 within 3h leads to cardiac rapture by formation of blood clot at the left ventricular infarct area. Donepezil 5mg/kg/day pretreatment reduced the LPS–induced MMP-9 expression from macrophages which infiltrate into the infarcted myocardium and reduce risk in left ventricular free wall rupture during the acute phase of MI also improves heart rate and systolic blood pressure.[30]

Liraglutide

It is an Glucagon-like peptide-1(GLP-1) receptor agonist[31], completed phase 3 clinical trial as an anti-diabetic drug to treat type-2 diabetes.[32] GLP-1 a member of proglucagon-derived pepdide family.[31] GLP-1R is expressed in the heart,

agonist of this receptor activates cardiomyocyte signalling pathways.[33] In an experimental model GLP-1 administration prevents the cardiac injury and ischemia.[34,35] In pilot study, administration of GLP-1 to human subjects with left ventricle dysfunction reduced hospitalization and improves the quality of life in both diabetic and non-diabetic patients having congestive heart failure.[36] Liraglutide(LIR) 75µg/kg,ip twice daily for 1 week has increased survival rate and reduced mortality also decreased cardiac repture in both diabetic and non- diabetic mice in which MI was previously induced by surgical ligation of left anterior descending artery and also decreases infarct size by inhibiting MMP-9 and it cleaved caspase 3 at the infract area. LIR activates cardioprotective genes such as Akt, Glycogen synthase kinase-3 beta (GSK3β), Peroxisome proliferator-activated receptor gamma (PPAR β-δ), Nuclear factor (erythroid-derived 2)-like 2 (NrF-2) and Heme oxygenase (HO-1) which are responsible for cardioprotection in ischemic injury. LIR 100nM increases cAMP of cardiomyocytes of mice in culture media. Liraglutide treatment *In vivo* prevented ischemia-reperfusion injury of isolated heart *ex vivo* by recovering left ventricle pressure load. All of these results revels that LIR is an promising repurposed drug to treat MI.[37]

CONCLUSION

Drug repurposing has emerged as an interesting field in MI research. This review concludes that pharmacological action of drugs such as Peroxetine (Selective serotonin reuptake inhibitor), Colchicine (anti- inflammatory drug), Donepezil (Acetylcholinesterase inhibitor) and Liraglutide (Glucagon-like peptide-1(GLP-1) receptor agonist) are the drugs with new indication for the treatment of myocardial infarction.

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